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Review

TNFRSF9 (TNF receptor superfamily member 9)

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Abstract

Review on TNFRSF9 (CD137), with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
TNFRSF9; CD137; tumor necrosis factor receptors; Immune response; T cell response.

Identity

Other names: CDw137, CD137, ILA

HGNC (Hugo): TNFRSF9

Location: 1p36.23

DNA/RNA

Description

CD137 is a member of the tumor necrosis factor receptor superfamily 9 (TNFRSF9) first identified in mice (Kwon 1989, Kwon 1994) and found to map to murine chromosome 4 at the 75.5 cM position. Schwarz et al. isolated a 1.4-kb full-length cDNA from a library constructed from activated human T-cell leukemia virus (HTLV) type 1-transformed human T-lymphocytes (Schwarz 1993). Schwarz et al. localized the CD137 gene to chromosome 1p36, a region that also harbors genes of several other members of this receptor family (e.g., TNFRSF1B (TNFR2), TNFRSF8 (CD30), TNFRSF4 (OX40) and TNFRSF25 (Apo3)) and is associated with deletions and rearrangements in several malignancies including neuroblastomas, myelodysplastic syndrome, and refractory acute non-lymphocytic leukemia (Schwarz 1997).

Human CD137 gene

Human CD137 consists of 255 amino acids with two potential N-linked glycosylation sites (Alderson 1994). Hydrophobicity analysis revealed amino acids 1-17 to be a putative signal peptide followed by an extracellular domain of 169 amino acids and then a transmembrane domain of 27 amino acids between positions 187-213 and lastly a short intracellular domain of 42 amino acids (Alderson 1994). The molecular weight of the protein was calculated to be 27 kDa (Zhou 1995) and was shown to be 60% identical to murine CD137 (Alderson 1994). Five regions of amino acid sequences were conserved between mice and human in the cytoplasmic domain an indication that these residues might be important for CD137 function (Alderson 1994). Murine and human CD137 ligands were identified and cloned by Alderson et al.(Alderson 1994).

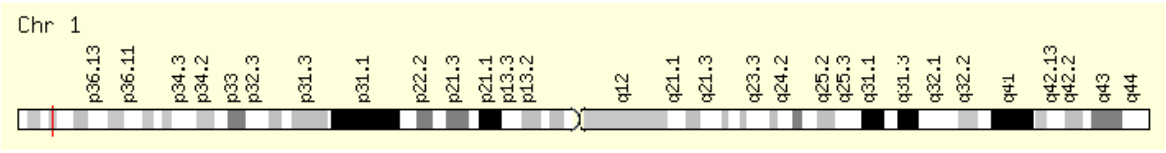

Figure 1. Mapping of CD137 gene on chromosome1p36 (from GeneCards CD137 gene).

The human TNFSF9 (CD137L) consisted of 254 amino acids and its gene maps to chromosome 19 in the region 19p13.3 (Alderson 1994). The human CD137-L shows 36% amino acid identity with its murine counterpart (Alderson 1994). High-affinity binding of huCD137 Fc to either native or recombinant human CD137-L was also demonstrated (Alderson 1994). The murine CD137 ligand consists of 309 amino acid polypeptide and its gene maps to murine chromosome 17 (Goodwin 1993).

Mouse CD137 gene

The CD137 gene in mice spans approximately 13kb and consists of 10 exons, two of them in the 50 untranslated regions and eight in the coding region (Kwon 1994). Nucleotide sequence analysis of CD137 showed a single open reading frame, which codes for a polypeptide 256 amino acids in length with a calculated molecular mass of 27.5kDa (Kwon 1994). The first 23 amino acids were shown to be a signal peptide, followed by a cysteine-rich region, which comprised of four potential TNFR motifs, of which the first was partial and the third distinct from those of the TNFR (Kwon 1994). Almost 30% of the amino acids residing between residues 140-185, a part that follows the ligand binding domain, were serine or threonines. These provide a potential site for O-linked glycosylation while amino acids 186-211 form the hydrophobic transmembrane domain which is followed by the stop-transfer sequence containing several basic residues (Kwon 1994).The carboxyl terminal part of the cytoplasmic domain contains two short runs of three and four acidic residues, respectively, and a sequence of five glycines followed by a tyrosine (Kwon 1994).

Transcription

CD137 was found to be induced on CD4+ and CD8+ T cells in mice and humans (Kwon 1989, Schwarz 1995, Vinay 1998, Pollok 1993). In mice, the expression takes several hours after stimulation, increases slowly, culminates at 60 hours and declines again by 110 hours (Goodwin 1993, Vinay 1998, Pollok1994). In humans, CD137 mRNA was detected 1.5 hours after stimulation on T lymphocytes, reaching maximal levels at 8 hours, and declining to background levels by 48 hours (Schwarz 1995).

Protein

Description

CD137 is a 30-kDa glycoprotein and exists as both a monomer and a 55-kDa dimer on the T cell surface (Kwon 1994).The CD137 gene encodes a 255-amino acid protein with 3 cysteine-rich motifs in the extracellular domain, a transmembrane region, and a short N-terminal cytoplasmic portion containing potential phosphorylation sites (Schwarz 1993).

Structure: Bitra et al.determined the crystal structure of mCD137 to 2.2 Å resolution and found that similar to other TNFRSFs, mCD137 has four cysteine rich domains (CRDs). However, the organization of CRD1 and the orientation of CRD3 and CRD4 with respect to CRD2 in the mCD137 structure distinctly differed from those of other TNFRSFs (Bitra 2017).

Expression

In humans, CD137 expression has been reported in follicular DCs (Lindstedt 2003), monocytes (Kienzle 2000), hepatoma cells (Schwarz 1995) and blood vessels from individuals with malignant tumors (Broll 2001). Expression of CD137 soluble form has been reported in the serum of patients with rheumatoid arthritis (Michel 1998). Incresed expression of CD137 in human peripheral blood mononuclear cells post exposure to mitomycin and other DNA damaging agents, such as doxorubicin, bleomycin and girradiation (Kim 2002). Expression of CD137L was observed following stimulation of professional antigen presenting cells (APCs) including dendritic cells (DCs) and macrophages as well as activated B cells in both human and mice (Alderson 1994, Goodwin 1993, Pollok 1994, Futagawa 2002, DeBenedette 1997). CD137 is also expressed by follicular DC, monocytes, mast cells, granulocytes, and endothelial cells (Anderson 2012). Anderson et al. described CD137 protein expression by follicular DC in the germinal center and scattered paracortical T cells, but not by normal germinal-center B cells, bone marrow progenitor cells, or maturing thymocytes. CD137 expression was also observed on activated natural killer (NK) (Malero 1998), dendritic cells (DC)(Futagawa 2002) as well as neutrophils (Heinisch 2000) in mice.

Localisation

Using immunohistochemical studies on human tissue samples to determine in vivo CD137 expression in non-immune tissue samples, Broll et al. found a strong CD137 expression in blood vessel walls, on the endothelial layer, and on the vascular smooth muscle cells.

Function

The CD137L-CD137 pathway is known to co-stimulate T cells to carry out effector functions such as eradication of established tumors (Melero 1997, Ye 2002) as well as the broadening of primary and memory $CD8^+$ T cell responses (Halstead 2002, Bertram 2002). Signals moderated by CD137 have been shown to induce a novel subpopulation of $CD11c^+$ $CD8^+$ T cells that have strong anti-cancer and anti-autoimmune effects (Vinay 2006). A novel carbohydrate-mediated interaction between CD137

and LGALS9 (Galectin-9 (Gal-9)) was identified and it was demonstrated in several immune responses that Gal-9 plays a significant role in CD137 signaling activities (Madireddi 2014). Gal-9 binds to terminal galactose moieties of N-linked glycans within the CRD4 region of CD137 and there is no competition between this binding with the binding of CD137 to its natural ligand CD137L or to agonist antibodies against CD137 (Bitra 2017). Bitra et al. also demonstrated that Gal-9 facilitates signaling and functional activation of CD137 in mouse T cells, DCs and NK cells upon binding mouse CD137L or agonist antibodies to CD137 (Bitra 2017). Once ligated and crosslinked, CD137 interacts with the tumor necrosis factor (TNF)-associated factors 1 and 2 (TRAF1 and TRAF2), a process that leads to activation of the master immuno-regulatory transcription factor NF-κB (Chester 2016). In T cells, CD137 signaling results into upregulation of the anti-apoptotic B-cell lymphoma-extra large (BCL2L1 (Bcl-xl)), B-cell lymphoma 2 (BCL2) pathways and induces proliferation and production of pro-inflammatory cytokines interferon gamma (IFNG (IFN-γ)) and IL2 (Lee 2002, Snell 2011). Additionally, CD137 stimulation causes an increase in signaling through the T-cell receptor (TCR) and amplifies the cytotoxicity of CD8+ T cells (Shuford 1997). Similarly, in NK cells, CD137 stimulation enhances proliferation, IFN-γ production, and cytolytic action (Melero 1998). In DCs, CD137 ligation speeds up maturation through upregulation of B7 co-stimulatory molecules (CD80 and CD86) and elevates survival and production of IL6 and IL12 (Kuang 2012). Anti-CD137 immunotherapy has recently shown promise as a treatment for solid tumors and lymphoid malignancies in preclinical models (Anderson 2012). The mode of action underlying CD137-mediated tumor regression consists of multiple, complimentary antitumor immune pathways. Mainly, CD137 agonism activates a potent, cytotoxic T-cell population that can infiltrate and lyse tumors (Curran 2013). In addition to direct tumor lysis, CD137 stimulation stimulates secretion of type 1 cytokines, creating an inflammatory, immunogenic cytokine milieu within the tumor microenvironment (Li 2003). Finally, CD137 ligation increases the secretion of perforin (PRF1), granzyme and activation of the Fas ligand (FASLG) effector system by both CD8+ T cells and NK cells (Morales-Kastresana 2013).

Implicated in

Asthma

Polte et al. used a murine asthma model to demonstrate how a single injection of an anti-CD137 (CD137) mAb prevents the development of airway hyper reactivity, eosinophilic airway inflammation, excessive mucus production, and elevated IgE during a 7 week observation period. They further established that the disease is completely reversed by anti-CD137 mAb administration (Polte 2006).

Human atherosclerosis

CD137 is expressed in human atherosclerosis and its activation promotes inflammation and disease development in murine atherosclerosis (Söderström 2014). Söderström et al. showed that the minor T allele of rs2453021 is associated with increased intima-media thickness in the common carotid artery and increased risk of incident non-cardiac vascular events, thus providing the first human genetic evidence for involvement of CD137 in atherosclerosis (Söderström 2014).

Crystalline silica-induced lung inflammation and fibrosis

Li et al. found that CD137 is induced in response to crystalline silica injury in lungs and that it is highly expressed during development of experimental silicosis. The CD137 pathway signaling was discovered to enhance inflammatory response and promote pulmonary fibrosis induced by crystalline silica (Li 2016).

Colorectal cancer

Dimberg et al. investigated whether CD137 and CD137L protein levels are altered in colorectal tumours compared with paired normal tissues. They examined CD137 and CD137L plasma levels from patients with colorectal cancer. Collectively, they observed a significant lower CD137L level in cancerous tissue compared with paired normal tissue and the difference in CD137L protein level was significantly lower in the colon cancer subgroup compared with paired normal colon tissue. In addition, an elevated CD137 protein level in the rectal cancer subgroup compared with paired normal rectal tissue was observed. Higher soluble CD137 protein concentration was detected in the plasma of patients with a tumour localised in the colon compared to those with a tumour localised in the rectum. A tendency of higher CD137L protein concentration in the plasma from patients with colon tumour localization was observed. They also observed a strong correlation between plasma concentrations of CD137 and CD137L proteins. Their work revealed how different expression levels of CD137 and CD137L in the colon and rectum may indicate that various mechanisms are involved in the pathogenesis of colorectal cancer and lead to dissimilar protective immunity (Dimberg 2006).

Crohn's disease

Maerten et al. investigated whether CD137/CD137L interactions might be involved in the pathogenesis of Crohn's disease (CD) and found

that CD137 expression on lamina propria LP cells in inflamed and to a lesser extend in non-inflamed gut tissue from CD patients. They also found elevated CD137 mRNA levels in intestinal CD tissue. Their results suggest that CD137/CD137L interactions contribute to the persistence of gut inflammation in CD (Maerten 2004).

Type 1 diabetes

Forsberg et al. reported suppression of type 1 diabetes (T1D) progression in NOD mice by CD137 deficiency. From their findings, blockage of the CD137-CD137 ligand interaction significantly delayed T1D onset in NOD mice and absence of CD137 or its interaction with CD137 ligand led to suppression of T1D progression. They also demonstrated that soluble CD137 produced by regulatory T cells contributed to their autoimmune-suppressive function in this model. Their results suggest that CD137 can either promote or suppress T1D development in NOD mice depending on where it is expressed (Forsberg 2017).

Hodgkin lymphoma

Anderson et al. showed that CD137 protein is expressed by a selected group of hematolymphoid tumors, including classical Hodgkin lymphoma, T-cell and NK/T-cell lymphomas, and follicular dendritic cells neoplasms (Anderson 2012).

Malignant and benign tumors

In the 32 healthy tissue samples they examined, none contained CD137-positive vessels while malignant tumors had a significantly enhanced frequency of CD137-expressing blood vessels (11/34). In benign tumors (2/14) and in inflammatory tissues (2/9) only a minority had CD137-expressing vessels (Broll 2001). Salih et al. described CD137 expression on various human carcinoma cell lines, on cells of solid tumors derived from these cell lines, and cells obtained from human tumors (Salih 2000).

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